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Efficacy of a New Heparan Sulfate Mimetic Dressing in the Healing of Foot and Lower Extremity Ulcerations in Type 2 Diabetes: A Case Series

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Abstract

A novel heparan sulfate glycosaminoglycan mimetic product for local application to promote wound healing (CACIPLIQ) has recently become available. It is a biophysical therapeutic product comprising a polysaccharide as an innovative biomaterial to accomplish mechanical tissue engineering and skin regeneration in the site of ulceration. We present a series of 12 patients with type 2 diabetes (4 men and 8 women; age 53-87 years; diabetes duration 8-25 years) having chronic resistance to therapy for foot and lower extremity ulcerations. CACIPLIQ was locally applied twice per week after careful debridement. Complete ulcer healing was accomplished in all patients after a mean treatment duration of 4.92 months (range = 2-12 months). The product was very well tolerated. In conclusion, these results, although preliminary, are encouraging and suggest adequate efficacy and safety of the new product in difficult-to-heal foot and lower extremity ulcerations in type 2 diabetes.

Keywords

biomimetic scaffold, diabetic foot, dressing, hydration, tissue engineering, ulceration

Diabetic foot ulcers (DFUs) may prove very difficult to heal.[1,2] Failure to heal increases the likelihood of infection,[2,3] ultimately threatening to result in amputation.[4-6] Hence, there has been considerable effort to improve treatment, for example, by new dressings and skin substitutes,[7] protease modulating matrix,[8] growth factor administration,[9,10] hyperbaric oxygen,[11] negative pressure therapy,[12] local antibiotic therapy,[13] therapeutic angiogenesis,[14] improved revascularization,[15] and progress in surgery.[16-18]

CACIPLIQ20 (CACIPLIQ, OTR3 Company, Paris, France) is a novel heparan sulfate glycosaminoglycan mimetic product for local application to promote wound healing.[19-21] There is evidence that it increases granulation, reduces inflammation, and accelerates healing in the experimental full-thickness excisional wound model.[19] A case series has shown that it is efficacious in leg ulcers with critical ischemia.[22] In diabetic rats, intramuscular administration improved wound healing.[21]

However, experience with CACIPLIQ in diabetic foot clinics is currently extremely limited. Therefore, the aim of this case series is to present our preliminary results with this product in difficult-to-heal DFUs and lower extremity ulcerations as part of routine treatment in the everyday clinical reality.

Patients, Methods, and Outcomes

This is a series of 12 patients (4 men, 8 women) with type 2 diabetes, who presented to the Diabetic Foot Clinics of 2 hospitals from the same country. They had long-standing DFUs (n = 9) or calf ulcerations (n = 3). Ulcers were defined as wounds penetrating through all skin layers.[23,24] All these lesions had proved resistant to best multi-expert therapy (including suitable dressings, antibiotic administration, and revascularization, as appropriate) for at least 4 months. Treatment resistance was defined as failure to achieve >30% size reduction in 4 weeks with therapy.

Patient age ranged between 53 and 87 years, and diabetes duration between 8 and 25 years (Table 1). Neuropathy was present in all patients and was the main underlying etiology (n = 11). In 2 patients, prior amputations had been carried out (Lisfranc's amputation in one,

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hallux amputation in one). Stable Charcot osteoarthropathy[25] was present in one patient. Patient and ulcer characteristics are summarized in Table 1. All ulcers were Wagner stage 2. Figure 1 shows the efficacy of CACIPLIQ therapy in a patient.

Neuropathy was diagnosed by the Neuropathy Disability Score (NDS), a standardized clinical examination procedure, and was defined as NDS ≥ 3.[26] Peripheral arterial disease (PAD) was evaluated by the ankle-brachial index (ABI), an established screening tool for PAD,[27] and it was defined as ABI < 0.9 in at least one leg.[28]

CACIPLIQ is commercially available in small vials accompanied by sterile gauzes. According to the manufacturer's instructions, one vial was opened for every application, and the fluid poured to the gauze, which was applied to the wound surface for 5 minutes. Then paraffin gauzes and off-loading dressings were applied. Each patient applied CACIPLIQ twice per week; before CACIPLIQ application, the ulcer area was carefully debrided. On the remaining days, paraffin gauzes and off-loading dressings were used. During patient follow-up, the response to treatment was evaluated; if the ulcer area reduction was clinically significant, the treatment was continued.

At the same time, patients were offered standardized treatment modalities. These included off-loading, proper debridement, and local wound care at the discretion of the treating physician.

Initial HbA1c values are presented in Table 1. During the course of treatment, there was an effort to improve glycemic control, where appropriate, at the discretion of the treating physician. Regrettably, however, we lack serial measurements of HbA1c.

Treatment efficacy is summarized in Table 1. In all patients, use of CACIPLIQ succeeded in achieving complete ulcer healing. Mean treatment duration was 4.92 months (range = 2-12 months). Patients were followed-up for 3 months, and there was no ulcer recurrence.

In all patients, CACIPLIQ was very well tolerated. Local adverse events (itching, swelling, rash, etc) were not seen. Similarly, generalized hypersensitivity reactions were not encountered.

Discussion

This case series shows very good efficacy of CACIPLIQ in achieving complete healing of foot and lower extremity ulcerations in type 2 diabetes. Wound closure was achieved after mean treatment duration of 4.92 months. Importantly, the new product was used in ulcers that had previously been resistant to best therapy for ≥4 months. Hence, despite the absence of a control group, the success in wound closure can be attributed to CACIPLIQ.

CACIPLIQ may be described as a *smart* biomimetic polymeric scaffold.[19,20] It does not contain any active pharmaceutical ingredient, but is a unique biophysical therapeutic product comprising a polysaccharide as an innovative biomaterial to accomplish in situ mechanical tissue engineering and, thereby, regeneration of skin tissue in the site of ulceration.[19,20] Its mode of action is explained by biophysics and thermodynamics approaches, that is, the degree of hydration, as based on the degree of hydration to provide protein protection and stable mechanical support.[29-31] Importantly, while hydration is necessary for wound healing, degree of protein hydration is associated with their function and chemical stability.[29-31] Indeed, excess protein hydration, which is related to times and duration of their exposure to water (twice per week), impairs their integrity and functionality.[20-22,29-31]

The strength of this report is the provision of real-world data from 2 diabetic foot clinics. To the best of our knowledge, this is the first clinical data on the efficacy and safety of CACIPLIQ in DFUs and calf ulcerations. The limitations may be outlined as follows. First, the number of patients was very small. Second, there was no control group with placebo or other comparator. The absence of a control group is due to the fact that this report is based on retrospective observation from a case series and not on a randomized controlled clinical trial. Third, the cost-effectiveness of CACIPLIQ was not evaluated, but this was beyond the scope of the present work. A final limitation is that HbA1c was measured only once at baseline. Indeed, more details on the stringency of glycemic control during the study would have been welcome.

The practical implications of our findings are that CACIPLIQ appears to be efficacious in promoting healing of difficult-to-treat ulcerations in the feet and calves of diabetic patients. It is also very safe in this use. Arguably, one may anticipate equal, if not superior, efficacy in usual, not treatment-resistant ulcerations. However, we need to learn more about appropriate patient selection and about the optimal stage of therapy to use this product. Indeed, whether it is best to apply it as an initial therapeutic choice or whether it is wise to reserve it for patients in whom prior therapy has failed is an issue that needs clarification. A cost-utility analysis would be helpful for this decision.

In conclusion, this case series has provided evidence on the efficacy and safety of CACIPLIQ in difficult-to-heal foot and lower extremity ulcerations in type 2 diabetes. The results are encouraging, and so further experience with this product in diabetic foot clinics is needed.

Table 1. Patient and Ulcer Characteristics.

No.	Sex	Age (Years)	DM Duration (Years)	HbA1c (%)	Therapy	Comorbidities	Ulcer Location	Surface Area (cm^2)	Ulcer Type	Duration of CACIPLIQ Treatment (Months)	Outcome
1	Male	60	7	7.6	Insulin + OHAs	CAD, dyslipidemia	Heels	1 × 1; 2.5 × 1	Neuropathic	7	Complete healing
2	Female	80	2	7.8	OHAs	Hypertension, CAD	Right foot dorsum	2.5 × 2	Neuropathic + venous insufficiency	4	Complete healing
3	Female	80	17	7.9	Insulin + OHAs	Hypertension	Right heel	0.5 × 2.5	Neuropathic	2	Complete healing
4	Female	87	22	7.5	Insulin + OHAs	Hypertension	Right calf (lateral)	4 × 3	Neuropathy + local trauma	3	Complete healing
5	Female	68	25	6	OHAs	Hypertension	Right calf (posterior)	10 × 4	Neuropathy + local trauma	12	Complete healing
6	Female	70	12	7.5	Insulin	Osteoporosis	Left calf	1.5 × 1.5	Neuropathy + trauma	4	Complete healing
7	Female	64	23	12	Insulin	Retinopathy, renal disease	Right foot plantar	2.5 × 2.5	Neuropathy + Charcot foot	7	Complete healing
8	Male	85	20	8	Insulin	CAD, PAD	Right lateral malleolus	2 × 1.5	Neuroischemic	5	Complete healing
9	Male	69	14	7.6	Insulin + OHAs	Hypertension, dyslipidemia	Left foot plantar (5 MTH)	1 × 1	Neuropathic	4	Complete healing
10	Female	80	25	7.3	Insulin	Hypertension, dyslipidemia	Right foot plantar	2 × 2	Neuropathic + prior Lisfranc amputation	4	Complete healing
11	Female	72	11	7.9	OHAs	Hypertension, dyslipidemia	Right foot plantar	1 × 1.5	Neuropathic+ prior hallux amputation	3	Complete healing
12	Male	53	8	9.4	Insulin	Hypertension, dyslipidemia, stroke, retinopathy	Left foot plantar (1 MTH)	1 × 1	Neuropathic	4	Complete healing

Abbreviations: CAD, coronary artery disease; DM, diabetes mellitus; MTH, metatarsal head; OHAs, oral hypoglycemic agents; PAD, peripheral arterial disease.

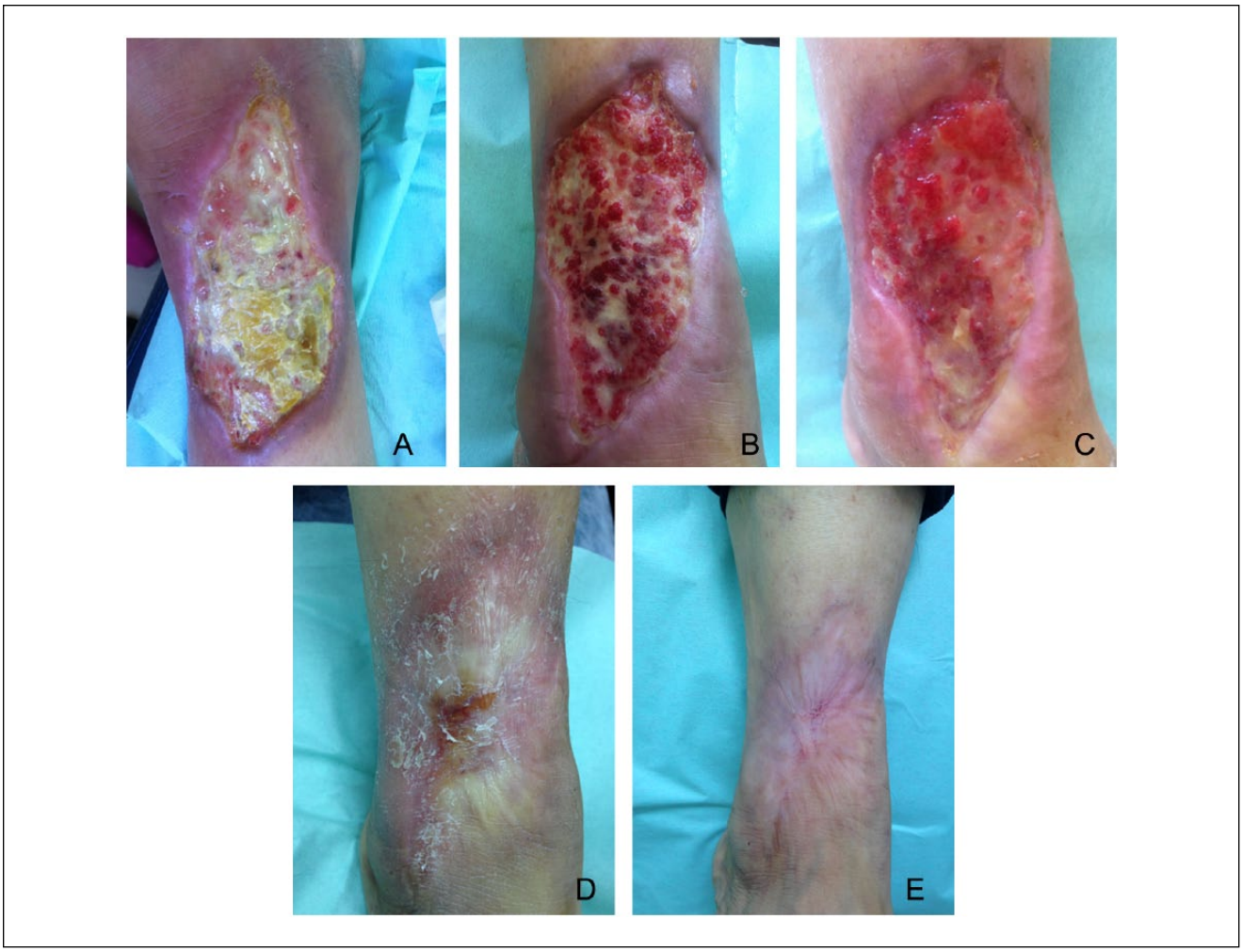

Figure 1. (A) Large ulceration on the posterior aspect of the right calf before CACIPLIQ treatment. (B) After 1 month of CACIPLIQ treatment. (C) After 2 months of CACIPLIQ treatment. (D) After 6 months of CACIPLIQ treatment. (E) Complete healing after 12 months of CACIPLIQ treatment.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Nikolaos Papanas has been an advisory board member of TrigoCare International, Astra-Zeneca, Boehringer Ingelheim, MSD, Novo Nordisk, and Pfizer; has participated in sponsored studies by Asta-Zeneca, GSK, Novo Nordisk, Novartis, and Sanofi-Aventis; has received honoraria as a speaker for Astra-Zeneca, Boehringer Ingelheim, Eli-Lilly, ELPEN, MSD, Mylan, Novo Nordisk, Pfizer, and Sanofi-Aventis; and attended conferences sponsored by TrigoCare International, Eli-Lilly, Galenica, Novo Nordisk, Pfizer, and Sanofi-Aventis. Nicholas Tentolouris has been an advisory board member of TrigoCare International; has participated in sponsored studies by Sanofi-Aventis, Eli-Lilly, MSD, Pfizer, Novo Nordisk, and Novartis; has received honoraria as a speaker for Astra-Zeneca, Eli-Lilly, Novo Nordisk, Novartis, and MSD; has received research support by Sanofi-Aventis and Novartis; and has attended conferences sponsored by Novo Nordisk, Sanofi-Aventis, Astra-Zeneca, MSD, and Novartis. Efstratios Maltezos has participated in sponsored studies by Asta-Zeneca, GSK, Novo Nordisk, Novartis and Sanofi-Aventis; and attended conferences sponsored by Wyeth, Pfizer, and Bayer. The other authors have no conflicts of interest to report.

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